Remarks

Claims 1-43 are pending. Applicants note with appreciation that claims 1-43 were found to be free of the art. Claims 1, 2, 4-8, 16, 18-22, 26, 27, 29, 31, 32, 33, 38 and 39 have been amended. Claims 28, 34, 35, 37 and 40-43 have been canceled. Support for the amendments can be found throughout the specification. No new matter has been added.

Cancellation and/or amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation and/or amendments to the claims are being made solely to expedite prosecution of one set of claims to subject matter of potential clinical and/or commercial significance. Applicants reserve the option to further prosecute additional claims, including without limitation claims of the same or similar scope as the claims formerly pending in the instant patent application.

Rejection of claims 1-43 under 35 U.S.C. § 112, first paragraph

Claims 1-43 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with the scope of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner acknowledges that the specification is enabling for a method of inhibiting calcineurin/NF-AT mediated transcription in cells and for inhibition of T cell proliferation. The claims have been amended to recite the inhibition of calcineurin/NF-AT mediated transcription or the inhibition of T cell proliferation. These amendments are believed to obviate the Examiner's rejection of the claims.

Regarding the Examiner's concern regarding the asserted criticality of expression level for the mutated MBP that may be required for the successful inhibition of transcription or proliferation in vivo, Applicants note the presence of a variety of examples in the literature of successful

expression of heterologous proteins in T cells leading to in vivo results. For instance, a number of groups have transduced T cells with an HSV tk construct for use in the event the T cell recipient develops GvHD. In those cases the non-MBP tk gene product acts as a suicide switch, triggered if necessary by the drug gancyclovir. In other cases T cells have been transduced with a Fas-FKBP construct, again for use in the event the T cell recipient develops GvHD. In that case, it is the Fas-FKBP fusion protein that acts as a suicide switch, triggered if necessary by a drug such as AP1903 which is capable of crosslinking a number of the fusion protein molecules. Successful in vivo experiments have been reported. See e.g., Bonini et al., Science 276:1719-1724, (1997); Verzeletti et al., Human Gene Therapy, 9:2243-2251 (1998); Thomis and Berg, J. Exp. Med 185:197-206 (1997); Spencer et al., Current Biology 6:839-847, (1996) (Exhibit A). In short, the literature describes heterologous expression in T cells leading successfully to positive in vivo results, including cases involving heterologous expression of genes for fusion proteins of the macrolide binding protein FKBP. Based on the literature, one skilled in this art would simply not expect any particular problem with achieving a sufficient heterologous expression level. Moreover, the MBPs useful in the practice of the invention are derived from a limited set of proteins, and therefore claims to methods using these proteins should not be considered unduly broad.

To summarize, the law requires merely that there be a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity. Here, Applicants have provided working examples showing that mutated MBPs expressed in cells bind to mutated macrolides and are biologically active. Based on these teachings, as well as the numerous scientific publications describing expression of proteins in T cells (including various MBPs) and the limited number of proteins involved, a person of skill in the art would reasonably anticipate expression of the mutated MBPs to lead to the claimed biological activity *in vivo*. Thus, since the relevant evidence as a whole shows the existence of a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, reconsideration of this rejection is respectfully requested.

In view of all of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Rejection of claims 31 and 40-43 under 35 U.S.C. § 112, second paragraph

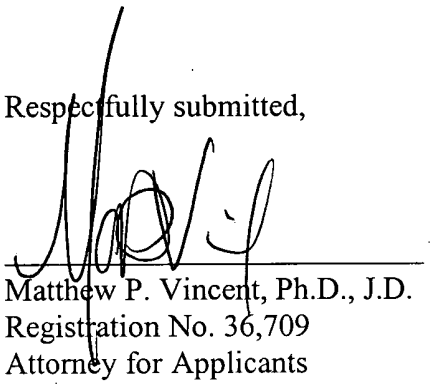
The Examiner rejected claims 31 and 40-43 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 31 has been amended and claims 40-43 have been canceled. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above remarks and the amendments to the claims, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Agent would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1299.

Respectfully submitted,



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